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Microglia role in the pain phenomenon

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A study published in the *Journal of the Brazilian Medical Association* examined the microglia role as the regulator of cognitive function[1]. Authors[1] reviewed what makes microglia so interesting to be studied as a possible therapeutic target in different conditions, starting with the analysis of its origins, passing through different conditions/diseases, and then discussing the possible future directions in research and clinic[1]. However, they[1] did not discuss the microglia role in the pain phenomenon as well as how it is related to cognitive function[2-4]. Therefore, as a contribution to the literature, we summarize the key findings on this topic (pain).

In neuropathic pain, microglia are morphologically and molecularly activated by opioids and contribute to opioid tolerance and dependence[5]. Activated microglia in the dorsal horn of the spinal cord are necessary for synaptic changes in this region and for pain hypersensitivity following nerve injury[6,7]. In addition, microglia are also activated in the brain and contribute to sensory and/or non-sensory (emotion, reward, and memory) aspects of neuropathic pain[5].

In chronic visceral pain, the mechanisms of microglia and astrocytes regarding the release of cytokines, chemokines, and neuroactive substances and the alteration of intracellular signaling pathways during the process are highlighted. As such, future perspectives include targeting microglia and astrocytes for chronic visceral pain treatment[8].

In chronic pain, microglia are indispensable for synaptic plasticity in the spinal dorsal horn and chronic pain[9]. Zhou et al.[9] showed that microglial colony-stimulating factor 1 and brain-derived neurotrophic factor signaling are essential for spinal long-term potentiation and chronic pain and that the microglia-dependent transition from synaptic potentiation to structural changes in pain pathways may underlie pain chronicity[9]. Besides, much scientific data suggest that classical activation of microglia in the spinal cord mediates neuroinflammation that plays an essential role in developing central sensitization and nociplastic pain[10].

In the early twentieth century, there was an increase in microglial studies in pain[11], with a particular focus on microgliosis in the spinal cord after nerve injury and in neuropathic pain[12]. We now know that signaling molecules are altered in microglia and contribute to the pathogenesis of pain; microglial mediators such as pro- and anti-inflammatory cytokines are potent neuromodulators that regulate synaptic transmission and pain via neuron-glial interactions; and microglia have an emerging role in pain resolution, in part via specialized pro-resolving mediators such as resolvins, protectins, and maresins[11].

Finally, pain, whether acute or chronic, involves inflammasome activation at the site of origin, the various relay stations, and the sensory and processing cortical areas[13]. Indeed, microglia are embedded in brain responses related to stress phenomena, the development of major depressive disorders (cognitive function), and pain-related neural processing[13]. However, there is a lack of robust or consistent clinical effects of microglial modulators due to the study designs and heterogeneity of the patient populations studied (or the underlying biology, of course)[11].

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REFERENCES

1. Sousa RAL, Cassilhas RC. Microglia role as the regulator of cognitive function. Rev Assoc Med Bras (1992). 2023;69(7):e20230412. https://doi.org/10.1590/1806-9282.20230412
2. Paudel A, Boltz M, Kuzmik A, Resnick B, Liu W, Holmes S. The association of cognitive impairment with depressive symptoms, function, and pain in hospitalized older patients with dementia. J Appl Gerontol. 2023;42(9):1974-81. https://doi.org/10.1177/07334648231168446
3. Pereira Nery ECH, Rocha NP, Cruz VT, Silva AG. Systematic review and meta-analysis on the association between chronic low back pain and cognitive function. Pain Pract. 2023;23(4):399-408. https://doi.org/10.1111/papr.13194
4. Peterson JA, Staud R, Thomas PA, Goodin BR, Fillingim RB, Cruz-Almeida Y. Self-reported pain and fatigue are associated with physical and cognitive function in middle to older-aged adults. Geriatr Nurs. 2023;50:7-14. https://doi.org/10.1016/j.gerinurse.2022.12.015
5. Inoue K, Tsuda M. Microglia in neuropathic pain: cellular and molecular mechanisms and therapeutic potential. Nat Rev Neurosci. 2018;19(3):138-52. https://doi.org/10.1038/nrn.2018.2
6. Tsuda M. Microglia in the spinal cord and neuropathic pain. J Diabetes Investig. 2016;7(1):17-26. https://doi.org/10.1111/jdi.12379
7. Tu Y, Muley MM, Beggs S, Salter MW. Microglia-independent peripheral neuropathic pain in male and female mice. Pain. 2022;163(11):e1129-44. https://doi.org/10.1097/j.pain.0000000000002643
8. Long JY, Wang XJ, Li XY, Kong XH, Yang G, Zhang D, et al. Spinal microglia and astrocytes: two key players in chronic visceral pain pathogenesis. Neurochem Res. 2022;47(3):545-51. https://doi.org/10.1007/s11064-021-03486-9
9. Zhou LJ, Peng J, Xu YN, Zeng WJ, Zhang J, Wei X, et al. Microglia are indispensable for synaptic plasticity in the spinal dorsal horn and chronic pain. Cell Rep. 2019;27(13):3844-59.e6. https://doi.org/10.1016/j.celrep.2019.05.087
10. Atta AA, Ibrahim WW, Mohamed AF, Abdelkader NF. Microglia polarization in nociplastic pain: mechanisms and perspectives. Inflammopharmacology. 2023;31(3):1053-67. https://doi.org/10.1007/s10787-023-01216-x
11. Chen G, Zhang YQ, Qadri YJ, Serhan CN, Ji RR. Microglia in pain: detrimental and protective roles in pathogenesis and resolution of pain. Neuron. 2018;100(6):1292-311. https://doi.org/10.1016/j.neuron.2018.11.009
12. Aldskogius H, Kozlova EN. Microglia and neuropathic pain. CNS Neurol Disord Drug Targets. 2013;12(6):768-72. https://doi.org/10.2174/18715273113126660168
13. Hoffmann S, Beyer C. A fatal alliance between microglia, inflammasomes, and central pain. Int J Mol Sci. 2020;21(11):3764. https://doi.org/10.3390/ijms21113764